ARIC Manuscript Proposal #3472

1. a. Full Title:
Associations of periodontal disease with small vessel disease and asymptomatic intracranial arterial atherosclerosis

b. Abbreviated Title (Length 26 characters):
Periodontal Disease association with Intracranial Small Vessel Disease and Large Vessel Atherosclerosis

2. Writing Group:
Writing group members:
Rachel Mascari, Souvik Sen, Univ of South Carolina, Columbia, SC; M. Fareed K Suri, Univ of Minnesota, Minneapolis, MN; Bruce Wasserman MD, Johns Hopkins, Baltimore, MD, Wayne Rosamond, Kevin Moss, James Beck, Univ. of North Carolina, Chapel Hill, NC; Rebecca F Gottesman, Johns Hopkins Univ, Baltimore, MD;

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.
_____ **[please confirm with your initials electronically or in writing]**

Corresponding authors: Rachel Mascari MS and Souvik Sen MD, MS, MPH, FAHA
Address: 8 Medical Park, suite 420 3390 Medical
              Park Road
              Phone:803.545.6073   Fax: 803.545.6051
              E-mail: souvik.sen@uscmed.sc.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
    Name: Wayne Rosamond PhD, MS
    E-mail: wayne_rosamond@unc.edu

3. Timeline: 09/04/2019 (proposal submission)
                10/30/2019 (data acquisition)
                12/30/2020 (manuscript submission)

4. Rationale:

Intracranial Atherosclerotic Stenosis (ICAS) is associated with 8% of all strokes in the U.S. Stroke patients with a higher risk of recurrent ischemic events caused by ICAS, reaching nearly 14% per year. [1] A community-based study conducted in China showed hs-CRP is an independent predictor of asymptomatic ICAS and intracranial atherosclerotic burden. In this study, after adjusting for possible risk factors, high level of hs-CRP (≥ 3 mg/l) remained significantly associated with asymptomatic ICAS (OR 1.28, 95% CI 1.02–1.61). [2] Extensive gingivitis, a reversible form of periodontal disease that is

associated with a high inflammatory index, has been shown to be significantly associated with systemic diseases as well as with the systemic inflammatory markers IL-6 and CRP [3].

Periodontal disease has previously been linked with stroke and extracranial carotid atherosclerosis. However, no studies to date have investigated the association between periodontal disease and intracranial atherosclerosis. In light of the important role of inflammation in intermediate stroke risk factors including atherosclerotic disease and potential for systemic inflammation caused by periodontal disease, investigating the relationship between PD and ICAS could identify a new risk factor for intracranial atherosclerosis.

Cerebral small vessel disease (SVD) manifests as white matter hyperintensities and contributes to ischemic stroke of the lacunar subtype. SVD causes 25% of ischemic stroke and more than doubles the odds of recurrent stroke [4]. However, its pathogenesis remains uncertain and risk factors are still being discovered. Prior studies have demonstrated an association between inflammation and specific types of SVD. [5] Since PD, a potentially modifiable risk factor, has been shown to be associated with inflammation [3], a relationship between PD and SVD could identify a new risk factor for cerebral SVD.

For this study, our objectives are i) to study the relationship between each class of periodontal status and severe asymptomatic ICAS, defined as ≥50% stenosis measured on magnetic resonance angiogram (MRA) and ii) to investigate the relationship between periodontal disease and intracranial small vessel disease assessed on magnetic resonance imaging (MRI) brain.

5.   Main Hypothesis/Study Questions:

Is periodontal disease (PD) independently associated with severe asymptomatic intracranial atherosclerotic stenosis (ICAS) and moderate-severe small vessel disease?

Subjects with a diagnosis of PD will have a higher proportion of severe asymptomatic ICAS. These subjects will also have a higher proportion of moderate-severe small vessel disease, manifested as white matter hyperintensities.
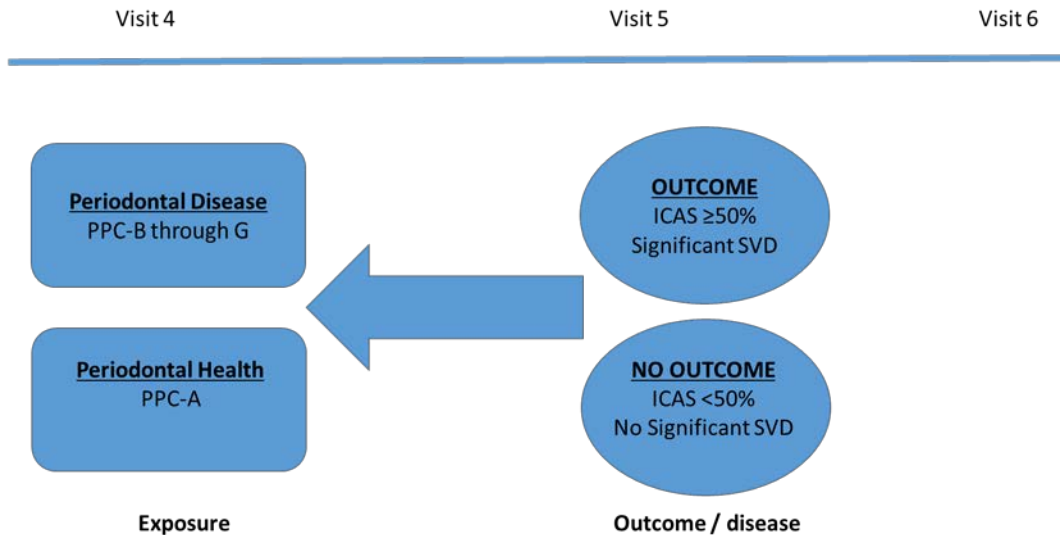
6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

1. **Study design: CASE-CONTROL**
   1) CASE-≥50% ICAS on MRA   CONTROL: <50% ICAS on MRA (visit 5)
   2) CASE-Significant WMD on MRI   CONTROL: No significant WMD on MRI (visit 5)

   EXPOSURE: PD (PPC) assessed on visit 4

CASE-CONTROL STUDY DESIGN

| | Visit 4 | Visit 5 | Visit 6 |

Periodontal Disease
PPC-B through G

Periodontal Health
PPC-A

Exposure

OUTCOME
ICAS ≥50%
Significant SVD

NO OUTCOME
ICAS <50%
No Significant SVD

Outcome / disease

Inclusion/Exclusion:

In the Dental Atherosclerosis Risk in Communities (Dental ARIC) study, full-mouth clinical periodontal measurements (7-indices) collected at 6 sites per tooth from 6,155 subjects without prior stroke were used to differentiate seven periodontal profile classes (PPCs: A or periodontal health, B through G based on increasing severity of periodontal disease). Of this cohort, a stratified subset underwent 3D time-of-flight MR angiogram and 3D high-isotropic resolution black blood MRI. ICAS was graded according to the criteria established by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial. For each subject, white matter disease (WMD) was measured for both the percentage and volume of white matter hyperintensities apparent on FLAIR MRI images. WMD was further classified into periventricular white matter hyperintensities (PVWMH) and deep white matter hyperintensities (DWMH). Only patients with MRI and MRA obtained during visit 5 will be included. Among these participants, those with missing dental history information and those who do not meet the criteria as above will be excluded. Those with race other than white or black will be excluded due to limited sample size.

Main exposure: PD was classified at visit 4. Details on the periodontal profile class (PPC) may be found elsewhere. [6] Briefly, participants were grouped into periodontal health (PPC-A), mild PD (PPC-B and C), moderate PD (PPC-D and E) and severe PD (PPC-F and G) groups. Among these groups, periodontal health (PPC-A) served as the comparison group. By definition, they were classified as PPC-A or periodontal health, PPC-B or mild periodontal disease, PPC-C or high gingival index score, PPC-D or tooth loss, PPC-E or posterior periodontal disease, PPC-F or severe tooth loss, and PPC-G or severe periodontal disease. PPC-A through G indicated higher grades of periodontal disease. The PPC is a data-driven agnostic classification system that does not utilize a priori assumptions of disease parameters to create seven different mutually-exclusive classes of disease that follow a gradient in terms of attachment loss, but not necessarily a gradient in clinical inflammation (ie, gingival index and bleeding scores).[6]

Main Outcomes:

- Severe Asymptomatic Intracranial Atherosclerotic Stenosis (0-50% stenosis, ≥50% stenosis)
- Cerebral White Matter Disease Volume (significant amount to be determined after data Obtained)

Co-variates: Age, gender, race (categorized as European American or African-American), and smoking status at visit 4 was assessed by self-report. Hypertension was defined as a systolic blood pressure of 140mmHg or higher, a diastolic blood pressure higher than 90mmHg, or use of medications to treat hypertension. Diabetes was determined by a self-reported history of a physician diagnosis of diabetes, non-fasting blood glucose level of 200 mg/dL or higher, fasting blood glucose level of 126mg/dL or higher (to convert glucose to millimoles per liter, multiply by 0.0555), or use of insulin or other oral hypoglycemic medications. LDL cholesterol was obtained from fasting lipid profile. [7]

Statistical analysis:

For the descriptive analysis, patient's demographic, medical history variables, and baseline clinical characteristics will be compared across ICAS categories. Chi square testing and independent sample t-test will be used for comparison of categorical and continuous variables, respectively.

Logistic regression models will be used to calculate odds ratios (ORs) of the effects of variables on the relationship between PD and ≥50% ICAS. Separate logistic regression models will be used to calculate ORs and 95% CIs for association of PD with ICAS after adjustment for multiple covariates. Several models may be run including covariates -- demographics (i.e. age, race, sex) and vascular risk factors (i.e. hypertension, LDL cholesterol, DM, smoking). These covariates will initially be assessed for evidence of significant confounding between the exposure and each outcome variable, before being included in a final model.

The analysis to test the relationship between PD and small vessel disease measured as the log of the white matter hyperintensities on MRI brain will be compared between the periodontal status categories using t-test, ANOVA and ANCOVA (after adjustment for covariates listed above). All statistical analyses will be two-tailed, and a P value of 0.05 will be considered for statistically significant.

Exposure Variable	Periodontal disease (PPC or periodontal profile class) assessed at V4
Outcome Variables	• ICAS (no stenosis, <50% stenosis, ≥50% stenosis/complete occlusion) measured at V5 • Moderate-severe white matter disease (DWMH and PVWMH) automated measurement (mm2) and log-transformed white matter hyperintensity volume, also measured on V5
Covariates	Sex Age Race Filed Center Hypertension

	Diabetes
	Smoking Status
	LDL
Analysis	Logistic regression (Univariable and Multivariate)

1. Limitation:

1. Traditionally, digital subtraction angiography (DSA) is regarded as the gold standard for the diagnosis of ICAS; however, it is expensive and invasive. Although MRA has been regarded as a minimally-invasive and convenient screening method to diagnose ICAS, it is not as accurate as digital subtraction angiogram for determining ICAS. Having said that, doing DSA in asymptomatic study participants would not be practical due to the risk associated with invasive procedure.
2. Periodontal disease: reliance on single periodontal disease assessment, a limited number of incident stroke subtypes, and owing to the observational nature of our investigation, the possibility of residual confounding cannot be eliminated. Socioeconomic factors such as access to care, income, and health-care behaviors may be potential confounders. However, we adjusted for education levels that in these data serve as a surrogate for the socioeconomic status.
3. The exposure measurement-periodontal status at V4 and outcome measurements-large vessel disease ICAS on MRA and small vessel disease on MRI performed on V5. The proposal is hence designed as a case-control study, and will serve the purpose of generating hypotheses by testing the associations. A prospective study may be planned based on the data to confirm hypothesis and any potential causal associations.

   This proposal has important clinical implications and may help point the way to future research to identify and target populations with ICAS and small vessel disease, both having high stroke risk. Hence, the results may help clinicians regarding stroke prevention strategy for high-risk populations, such as periodontal treatment.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes   __x_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? _____ Yes   _____ No (NA)

8.a. Will the DNA data be used in this manuscript? _____ Yes   __x_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _____ Yes   _____ No (NA)

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to

the publications lists under the Study Members Area of the web site at:
http://www.cscc.unc.edu/ARIC/search.php

___x__ Yes   _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Elter JR, Champagne CME, Offenbacher S, Beck JD. 2004. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease.. J Periodontol. 75(6):782-90.

Beck JD, Eke P, Heiss G, Madianos P, Couper D, Lin D, Moss K, Elter J, Offenbacher S. 2005. Periodontal disease and coronary heart disease: a reappraisal of the exposure.. Circulation. 112(1):19-24.

Qiao Y, Guallar E, Suri FK, Liu L, Zhang Y, Anwar Z, Mirbagheri S, Xie YYJoyce, Nezami N, Intrapiromkul J et al.. 2016. MR Imaging Measures of Intracranial Atherosclerosis in a Population-based Study. Radiology. 280(3):860-8.

Suri M, Fareed K, Qiao Y, Ma X, Guallar E, Zhou J, Zhang Y, Liu L, Chu H, Qureshi AI, Alonso A et al.. 2016. Prevalence of Intracranial Atherosclerotic Stenosis Using High-Resolution Magnetic Resonance Angiography in the General Population: The Atherosclerosis Risk in Communities Study.. Stroke. 47(5):1187-93.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x_ Yes   ____ No

11.b. If yes, is the proposal
_X_   A. primarily the result of an ancillary study (list number*1996.01, 2009.27**)**
___   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)
*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts

should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

References:

1. Suri M, Fareed K, Qiao Y, Ma X, Guallar E, Zhou J, Zhang Y, Liu L, Chu H, Qureshi AI, Alonso A et al.. 2016. Prevalence of Intracranial Atherosclerotic Stenosis Using High-Resolution Magnetic Resonance Angiography in the General Population: The Atherosclerosis Risk in Communities Study. Stroke. 47(5):1187-93.
2. Wang J1, Liu Y, Zhang L, Li N, Wang C, Gao X, Zhou Y, Wang A, Wu S, Zhao X. Associations of high sensitivity C-reactive protein levels with the prevalence of asymptomatic intracranial arterial stenosis. Eur J Neurol. 2014;21(3):512-8
3. Beck, JD, Moss, KL, Morelli, T, Offenbacher, S. Periodontal profile class is associated with prevalent diabetes, coronary heart disease, stroke, and systemic markers of C-reactive protein and interleukin-6. *J Periodontol.* 2018; 89: 157– 165. https://doi.org/10.1002/JPER.17-0426
4. Nam K-W, Kwon H-M, Lim J-S, Han M-K, Nam H, Lee Y-S (2017) The presence and severity of cerebral small vessel disease increases the frequency of stroke in a cohort of patients with large artery occlusive disease. PLoS ONE 12(10): e0184944. https://doi.org/10.1371/journal.pone.0184944
5. Men X, Li J, Zhang B, Zhang L, Li H, Lu Z. Homocysteine and C-reactive protein associated with progression and prognosis of intracranial branch atheromatous disease. PLoS One. 2013 Sep 11;8(9):e73030. doi: 10.1371/journal.pone.0073030. eCollection 2013.
6. Morelli T, Moss KL, Beck J, Preisser JS, Wu D, Divaris K, Offenbacher S. Derivation and validation of the periodontal and tooth profile classification system for patient stratification. J Periodontol. 2017;88:153–165.
7. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129(4):687-702.